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## Total Synthesis of Kingianins A, D, and F\*\*‡

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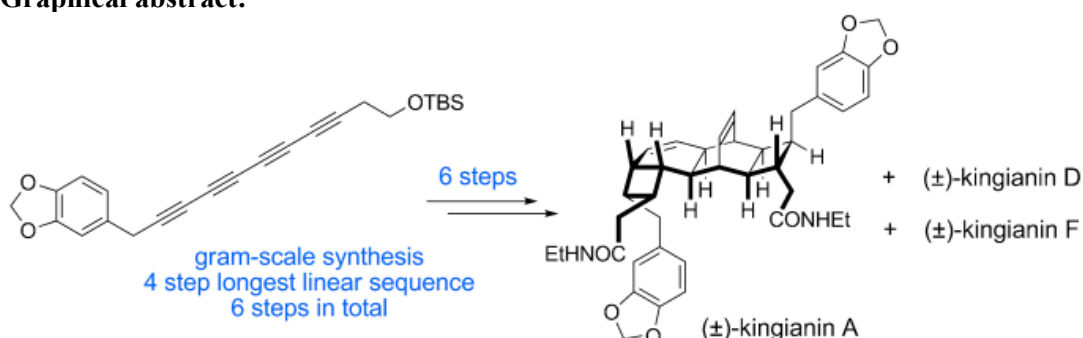
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<sup>[‡]</sup>In Memory of Rodney W. Rickards.

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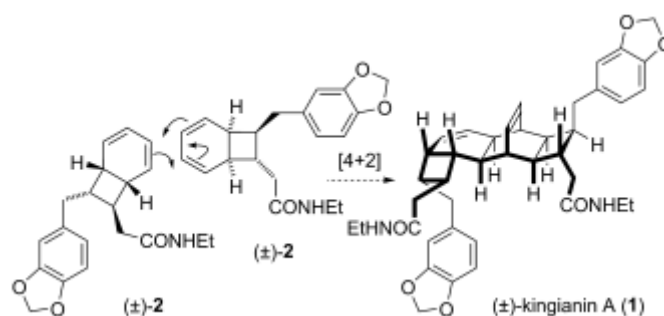
biomimetic synthesis; domino reactions; natural products; polyynes; radical cations

## Abstract

**A synthesis fit for a king:** The total synthesis of ( $\pm$ )-kingianins A, D, and F has been achieved in ten steps. Key features include the gram-scale synthesis and partial reduction of a conjugated tetrayne to a ( $Z,Z,Z,Z$ )-tetraene, the domino  $8\pi$ – $6\pi$  electrocyclic ring closure of a ( $Z,Z,Z,Z$ )-tetraene, and the radical-cation-catalyzed formal Diels–Alder dimerization of functionalized bicyclo[4.2.0]octadiene precursors.

## Main text

The kingianin natural products are a unique group of complex racemic bicyclo[4.2.0]octadiene dimers, isolated from the bark of *Endiandra kingiana* (Lauraceae) by Litaudon and co-workers.<sup>[1]</sup> The first reported kingianin, ( $\pm$ )-kingianin A (**1**),<sup>[1a]</sup> formulates as a dimer of bicyclo[4.2.0]octadiene **2**, and the Litaudon group proposed a biosynthesis involving spontaneous (non-enzyme-mediated) Diels–Alder dimerization (Scheme 1).<sup>[1]</sup> Several reports, however, describe the need for temperatures in excess of 150 °C for Diels–Alder dimerization of 1,3-cyclohexadiene.<sup>[2]</sup> The notion that a structural feature within compound **2** may lower the barrier to thermal Diels–Alder dimerization was investigated by Moses and co-workers in 2011.<sup>[3]</sup> An elegant synthesis of monomer **2** was achieved by the Moses group, but all attempts to induce thermal dimerization failed.<sup>[3]</sup> Inspired by the pioneering work of Bauld and co-workers,<sup>[4]</sup> we hypothesized that a radical cation Diels–Alder dimerization could explain the formation of the kingianins in nature.



**Scheme 1.** Diels–Alder biosynthetic pathway to ( $\pm$ )-kingianin A (**1**), as proposed by Litaudon et al.<sup>[1]</sup>

The bicyclo[4.2.0]octadiene framework present within Litaudon's proposed biosynthetic monomer **2** is a skeletal feature found in several natural products.<sup>[5–9]</sup> The endiandric acids, which were isolated in racemic form in the early 1980s by Black and colleagues, were the first reported examples.<sup>[5]</sup> Black proposed that the bicyclo[4.2.0]octadiene structure was formed through a spontaneous  $8\pi$ – $6\pi$  domino electrocyclization of either an ( $E,Z,Z,E$ )-tetraene or a ( $Z,Z,Z,Z$ )-tetraene (Scheme 2).<sup>[5b–f]</sup> Beautiful biomimetic syntheses of various

bicyclo[4.2.0]octadiene natural products by Nicolaou,<sup>[10]</sup> Trauner,<sup>[11]</sup> Baldwin,<sup>[12]</sup> Parker,<sup>[13]</sup> and Moses<sup>[14]</sup> have successfully utilized the proposed (*E,Z,Z,E*)-tetraene precursors. Evidently, the difficulty associated with preparing conjugated all-(*Z*)-polyenes has precluded their use in synthesis. In fact, (2*Z*,4*Z*,6*Z*,8*Z*)-decatetraene is both the highest all-(*Z*)-conjugated polyene and the only (*Z,Z,Z,Z*)-tetraene synthesized thus far.<sup>[15]</sup>

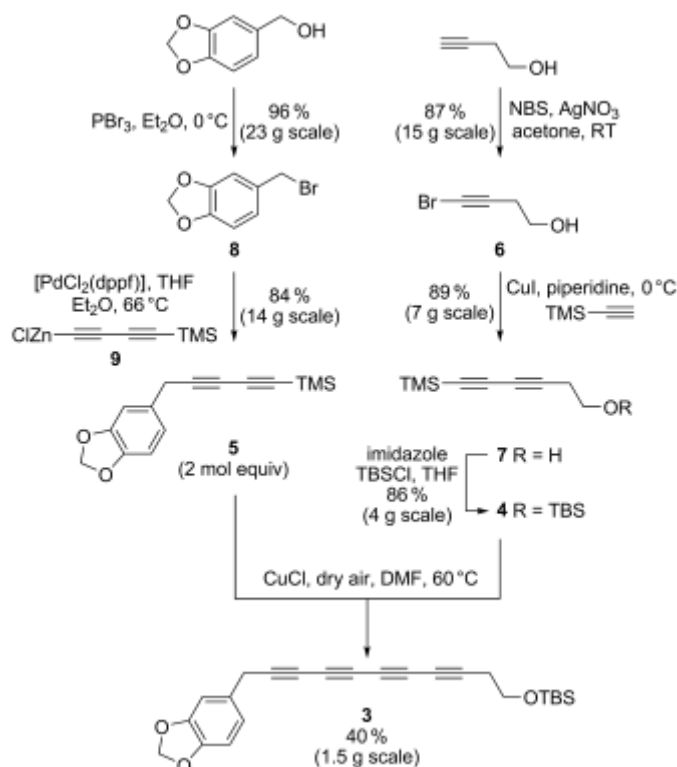
Given the unprecedented structure and puzzling biosynthetic origin of the kingianin natural products,<sup>[1]</sup> we decided to embark upon efforts towards their synthesis. The wealth of synthetic work in the literature utilizing (*E,Z,Z,E*)-tetraene precursors to access bicyclo[4.2.0]octadiene structures<sup>[3, 10–14]</sup> convinced us that we should take this opportunity to investigate the alternative biosynthetic precursor, namely the (*Z,Z,Z,Z*)-tetraene (Scheme 2).<sup>[5b–f]</sup> Although initially drawn to the  $sp^2$ – $sp^2$  cross-coupling strategy utilized by Negishi for the synthesis of (*Z,Z,Z*)-trienes,<sup>[16]</sup> we elected instead to investigate the feasibility of a four-fold stereoselective partial reduction of a conjugated tetrayne. We anticipated that if this unprecedented<sup>[17]</sup> and highly challenging<sup>[18]</sup> synthetic transformation were realized then a remarkably short synthesis of the kingianins could be achieved.



**Scheme 2.** The  $8\pi$ – $6\pi$  biosynthesis of bicyclo[4.2.0]octadiene structures, as proposed by Black et al.<sup>[5b–f]</sup>

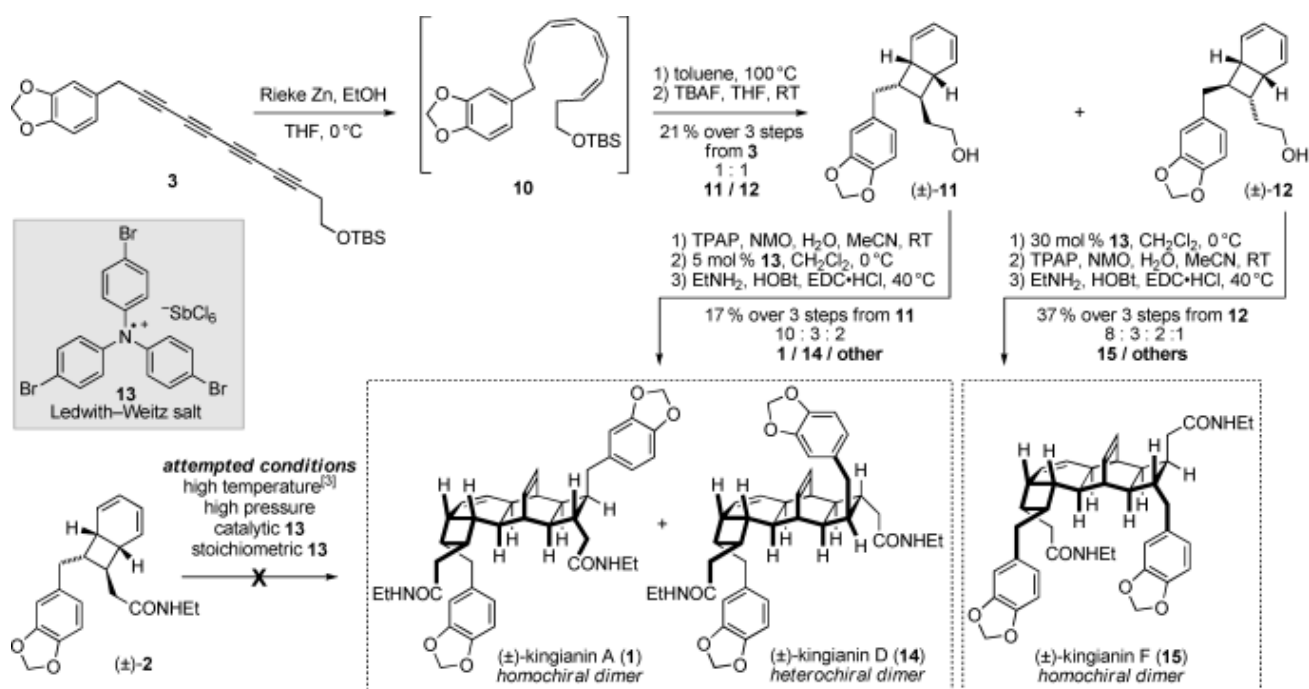
The application of previously reported methods<sup>[19]</sup> for the synthesis of unsymmetrical tetraynes was met with great difficulties. The instability of the requisite intermediates and problems associated with scaling up these approaches led us to develop a new scalable synthesis of unsymmetrical tetraynes. It is well known that steric bulk can stabilize polyene structures.<sup>[20]</sup> We took advantage of this fact by targeting TBS-protected (TBS=*tert*-butyldimethylsilyl) alcohol tetrayne **3**,<sup>[21]</sup> using Mori–Hiyama conditions for TMS-alkyne (TMS=trimethylsilyl) dimerization,<sup>[22]</sup> thereby avoiding unstable halogenated and terminal polyynes. The two requisite diynes **4** and **5** were successfully prepared in three and two steps, respectively, on a multi-gram scale (Scheme 3). Thus, an Alami modified<sup>[23]</sup> Cadiot–Chodkiewicz coupling of known bromobutynol **6**<sup>[24]</sup> with ethynyltrimethylsilane afforded TMS-diyne **7**, which was converted into TBS-ether **4** under standard conditions.<sup>[25]</sup> Meanwhile, known benzyl bromide **8**<sup>[26]</sup> was employed in a Negishi reaction<sup>[27]</sup> with organozinc reagent **9**,<sup>[28]</sup> which was derived from 1,4-bis(trimethylsilyl)buta-1,3-diyne.<sup>[29]</sup> Following extensive optimization, tetrayne **3** was isolated in 40 % yield on a gram scale.<sup>[30]</sup> This is the first reported crossed Mori–Hiyama coupling reaction<sup>[22]</sup> and the first gram-scale synthesis of an unsymmetrical tetrayne.<sup>[19]</sup>

With significant quantities of tetrayne **3** now available, investigation into the daunting four-fold reduction could begin.<sup>[17, 18]</sup> Following extensive experimentation, it was found that Rieke zinc in ethanol afforded (*Z,Z,Z,Z*)-tetraene **10** in a completely chemoselective and highly diastereoselective manner (Scheme 4).<sup>[17, 31]</sup> A solution of tetraene **10** in toluene was immediately heated to 100 °C, which triggered the domino 8 $\pi$ –6 $\pi$  electrocyclization sequence.<sup>[32]</sup> Following deprotection, the two diastereomeric alcohols **11** and **12** were isolated in a combined yield of 21 % from tetrayne **3** (Scheme 4).



**Scheme 3.** Gram-scale synthesis of unsymmetrical tetrayne **3**. dppf=1,1'-bis(diphenylphosphino)ferrocene, NBS=*N*-bromosuccinimide, TBS=*tert*-butyldimethylsilyl, TMS=trimethylsilyl.

We were delighted to find that both alcohols **11** and **12** underwent fast radical cation Diels–Alder dimerizations using catalytic quantities of the Ledwith–Weitz aminium salt, (*p*-BrC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>N<sup>+</sup>·SbCl<sub>6</sub><sup>−</sup> (**13**; Scheme 4).<sup>[33]</sup> Amide **2**, the proposed biosynthetic precursor to (±)-kingianin A (**1**),<sup>[1a]</sup> failed to dimerize under these reaction conditions (Scheme 4).



**Scheme 4.** Completion of the total synthesis of (±)-kingianins A, D, and F. EDC=1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, HOBt=hydroxybenzotriazole, NMO=*N*-methylmorpholine-*N*-oxide, TBAF=tetrabutylammonium fluoride, TPAP=tetrapropylammonium perruthenate.

The synthesis of (±)-kingianins A (**1**) and D (**14**) was eventually optimized to a sequence involving oxidation of alcohol **11** using the tetrapropylammonium perruthenate/ *N*-methylmorpholine-*N*-oxide (TPAP/NMO) conditions of Stark et al.,<sup>[34]</sup> with the product directly subjected to radical cation Diels–Alder dimerization using the Ledwith–Weitz salt (**13**; 5 mol %).<sup>[4, 33]</sup> The resultant mixture of diastereomeric diacids was directly converted into the corresponding diamides. Column chromatography afforded a mixture of three dimeric diamides in 17 % yield over the three steps from alcohol **11**. Reverse-phase preparative HPLC allowed the isolation of analytically pure samples of (±)-kingianin A (**1**), (±)-kingianin D (**14**) and a third, as yet undetermined, structure.<sup>[1]</sup> This radical cation Diels–Alder dimerization is a remarkably selective reaction, with only three of the potential thirty-two isomeric products isolated. Both (±)-kingianin A (**1**), a homochiral dimer, and (±)-kingianin D (**14**), a heterochiral dimer, are the result of *endo*-selective formal Diels–Alder reactions occurring at the convex faces of both diene and dienophile. Previous studies have shown that the radical cation Diels–Alder dimerization of 1,3-cyclohexadiene is *endo* selective,<sup>[4]</sup> however, a full explanation of the site and orientational regioselectivity observed in the present study will require further investigation. The natural product (±)-kingianin F (**15**) was similarly obtained by dimerization of the other bicyclo[4.2.0]octadiene diastereomer **12**, followed by double oxidation and diamide formation.<sup>[35]</sup>

In summary, our highly divergent biomimetic strategy has resulted in the total synthesis of ( $\pm$ )-kingianins A (**1**), D (**14**) and F (**15**), in a longest linear sequence of ten steps. The noteworthy synthetic aspects of our successful approach include the gram-scale preparation of an unsymmetrical tetrayne, the unprecedented reduction of a conjugated tetrayne to a (*Z,Z,Z,Z*)-tetraene, and radical cation Diels–Alder dimerization of functionalized bicyclo[4.2.0]octadienes. From these studies, we conclude that the kingianins are not formed through spontaneous Diels–Alder dimerization. Instead, we propose that nature uses a SET-mediated cycloaddition analogous to the approach described herein.<sup>[36, 37]</sup> Our results, in conjunction with previous biomimetic syntheses,<sup>[3, 10–14]</sup> demonstrate that (*E,Z,Z,E*)-tetraenes, and not their all-(*Z*) congeners,<sup>[32]</sup> are the likely biosynthetic precursors to bicyclo[4.2.0]octadiene natural products.<sup>[38]</sup>

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